BRIEF COMMUNICATION

Acute Myeloid Leukemia Following Hodgkin Lymphoma: A Population-Based Study of 35 511 Patients

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Treatments for Hodgkin lymphoma are associated with large relative risks of acute myeloid leukemia (AML), but there are few estimates of the excess absolute risk (EAR), a useful measure of disease burden. One-year Hodgkin lymphoma survivors (N = 35 511) were identified within 14 population-based cancer registries in Nordic countries and North America from January 1, 1970, through December 31, 2001. We used Poisson regression analysis to model the EAR of AML, per 10 000 person-years. A total of 217 Hodgkin lymphoma survivors were diagnosed with AML (10.8 expected; unadjusted EAR = 6.2; 95% confidence interval = 5.4 to 7.1). Excess absolute risk for AML was highest during the first 10 years after Hodgkin lymphoma diagnosis but remained elevated thereafter. In subsequent analyses, adjusted for time since Hodgkin lymphoma diagnosis and presented for the 5–9 year interval, the EAR was statistically significantly (*P*<.001) larger in patients diagnosed with Hodgkin lymphoma at age 35 years and older than in those diagnosed before 35 years of age. The EAR of AML declined statistically significantly after 1984 (7.0 to 4.2 and 16.4 to 9.9 in the <35 and ≥35 age groups, respectively), which may be associated with modifications in chemotherapy. [J Natl Cancer Inst 2006;98:215–8]

Treatments for Hodgkin lymphoma have resulted in excellent survival rates but are associated with large, increased relative risks of acute myeloid leukemia (AML) *(1–8)*. However, few estimates of the excess absolute risk (EAR), a useful measure of disease burden in a population *(9)*, exist; most *(1,4,5,7)*, but not all studies *(10)*, have been based on relatively small numbers of AML. No large, population-based investigation has estimated the EAR of AML following Hodgkin lymphoma, simultaneously evaluating the effects of age, calendar year of Hodgkin lymphoma diagnosis, time since Hodgkin lymphoma diagnosis, and initial treatment. It is of particular interest to determine whether applications of newer treatments are reflected in a decreased absolute risk of AML among Hodgkin lymphoma survivors in the general population.

One-year survivors (N = 35 511) of Hodgkin lymphoma who were diagnosed between January 1, 1970, and December 31, 2001, were identified within 14 population-based cancer registries in Denmark, Finland, Norway, Ontario, Sweden, and the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. Study dates varied slightly according to registry: Ontario, 1970–2000; Denmark, 1970–1998; Finland and Sweden, 1970–2001; Norway, 1970–1999; and the SEER Program, 1973–1999 (Connecticut [1973+], Hawaii [1973+], Iowa [1973+], New Mexico [1973+], and Utah [1973+], and the metropolitan areas of San Francisco–Oakland [1973+], Detroit [1973+], Seattle–Puget Sound [1974+], and Atlanta [1975+]). Analyses were restricted to 1-year survivors to permit a sufficient latent period for the development of therapy-related leukemias *(11)*. All registries collect demographic information and vital status at last follow-up. Except Sweden and Ontario, all registries also record the type of initial cancer treatment, which we categorized as radiotherapy alone (RT), chemotherapy alone (CT), radiotherapy and chemotherapy (RT + CT) or other/unknown. Detailed data with regard to initial treatment regimens (e.g., cytotoxic drug names and doses) were not available from the registry files, nor was information on subsequent therapy. Patients diagnosed with AML at least 1 year after Hodgkin lymphoma were identified through a search of cancer registry incidence files. Population-based incidence data for acute leukemia, not otherwise specified (AL–NOS) show age-specific trends that are strikingly similar to those of AML *(12)*. Thus, we grouped the 15 patients with AL–NOS with the 202 patients with AML *(13)*, and for simplicity, later refer to the category as AML. Small numbers (n = 13) of acute lymphoblastic leukemia (ALL) precluded analysis of this disease category.

Person-years (PY) and AML patients were categorized by calendar year of Hodgkin lymphoma diagnosis (1970–1984, 1985–2001), initial treatment, registry, and by 5-year intervals of attained age, calendar year, time since Hodgkin lymphoma diagnosis, and age at Hodgkin lymphoma diagnosis. Accumulated person-years at risk for each category defined by registry, sex, and 5-year age and calendar year intervals were multiplied by the corresponding AML incidence rates to calculate the number of expected cases in each category. O_i, E_i, and PY_i, denote observed cases, expected cases, and person-years in a specific category i, respectively.

The general Poisson regression methods used in this study have been described previously *(14)* and were implemented

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See "Notes" following "References."

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Table 1. Excess absolute risk (EAR)* of acute myeloid leukemia (AML)† following Hodgkin lymphoma

Characteristic	Calendar year of Hodgkin lymphoma diagnosis	All patients (N = 35 511)		Any chemotherapy (n = 12 196)‡§		Radiotherapy only (n = 8241)§	
		No. AML	EAR (95% CI)	No. AML	EAR (95% CI)	No. AML	EAR (95% CI)
All patients‖	N/A	217	8.3 (6.8 to 10.1)	83	11.3 (8.5 to 14.7)	40	5.4 (3.7 to 7.7)
Age at Hodgkin lymphoma diagnosis, y							
<35 (n = 19 742)	1970–1984	56	7.0 (5.2 to 9.1)	20	10.7 (6.9 to 15.9)	11	3.2 (1.6 to 5.7)
	1985–2001	34	4.2 (3.0 to 5.8)	13	4.8 (2.9 to 7.6)	2	1.6 (0.6 to 3.6)
≥35 (n = 15 769)	1970–1984	85	16.4 (12.5 to 21.0)	30	27.6 (18.7 to 39.5)	20	14.3 (8.7 to 22.1)
	1985–2001	42	9.9 (7.2 to 13.4)	20	12.4 (7.9 to 18.8)	7	7.0 (2.9 to 13.8)

*Based on the model shown in the text. EAR = excess number of cases per 10 000 person-years. Risk estimates presented for 5- to 9-year period after diagnosis of Hodgkin lymphoma. CI = confidence interval; N/A = not applicable.

†The category of AML includes 15 patients with acute leukemia, not otherwise specified, as described in the text.

‡Any chemotherapy = chemotherapy alone or chemotherapy given with radiotherapy.

§Numbers include only those patients reported to registries that collect data on initial course of cancer treatment (the National Cancer Institute's Surveillance, Epidemiology, and End Results Program and cancer registries in Denmark, Finland, and Norway).

‖Estimates not adjusted for age or calendar year of Hodgkin lymphoma diagnosis.

with the AMFIT module of the software package EPICURE *(15)*. An objective was to obtain estimates of the EAR and confidence intervals (CIs) for categories defined by age at Hodgkin lymphoma diagnosis (designated by a; a = 1 for age < 35 years; 0 otherwise) and calendar year of diagnosis (designated by c; c = 1 for 1985+; 0 otherwise) with adjustment for time since diagnosis (designated by t and expressed in years). The adjustment for t was important for evaluating calendar year effects given the shorter follow-up for Hodgkin lymphoma patients diagnosed after 1984. Another objective was to describe the pattern of risk over time. Results shown in Table 1 and Fig. 1 were based on a model in which the statistical expectation of $O_{a,c,t}$ was assumed to be

$$E_{a,c,t} + PY_{a,c,t} EAR(a, c, t)$$

with the logarithm of EAR (a, c, t) expressed as a linear function of a, e, t, and t^2. The EAR is expressed per 10 000 person-years. Analyses using continuous variables were based on midpoints of 5-year intervals. This model was chosen because it was the simplest model providing an adequate fit to the data. Specifically, expression of the EAR using age at Hodgkin lymphoma diagnosis as a categorical variable (with two categories) fitted the data better than expression of the EAR as a continuous function based on finer categories of age at Hodgkin lymphoma diagnosis, and a linear–quadratic function for time since Hodgkin lymphoma diagnosis fitted the data statistically significantly better than a linear model (P = .003). Because the EAR depended strongly on t, it was necessary to present results in Table 1 for a specific period, chosen to be the 5–9 year interval (t = 7.5), although all data contribute to the analyses. Analyses that allowed parameters to depend on initial treatment (RT only or with any chemotherapy [CT or RT + CT]) were also conducted. Calendar year of Hodgkin lymphoma diagnosis served as a surrogate for treatment era: mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) *(16)* was the primary chemotherapy regimen used between 1970 and 1984, whereas other regimens gained more widespread use in later years *(17–21)*. Sex was not included in the model because there was little evidence that any of the parameters depended on sex. All statistical tests were two-sided, and P<.05 was considered statistically significant.

Compared with 10.8 expected, 217 cases of AML were diagnosed (overall, unadjusted EAR = 6.2, 95% confidence interval [CI] = 5.4 to 7.1; observed/expected = 20.2, 95% CI = 17.6 to 23.0). During the 1–4, 5–9, 10–14, and 15+ year periods following Hodgkin lymphoma diagnosis, 92, 87, 29, and nine cases occurred (median = 5.9 years; range = 1 to 33 years). The EAR of AML was highest during the first 10 years after Hodgkin lymphoma diagnosis (EAR = 7.9, 95% CI = 6.8 to 9.3); risks were comparable during the 1–4 and 5–9 year periods. During the 10–14 year period, the EAR was lower but remained statistically

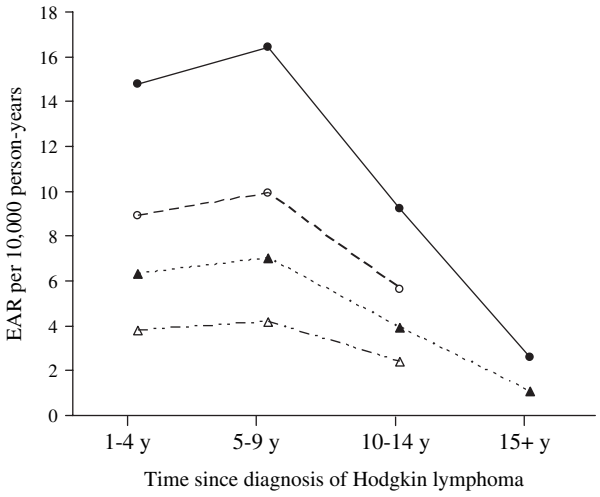

Fig. 1. Excess absolute risk of acute myeloid leukemia per 10 000 person-years (including 15 patients with acute leukemia, not otherwise specified, as described in the text) by time since diagnosis of Hodgkin lymphoma. Excess absolute risk after 14 years is not available for patients diagnosed with Hodgkin lymphoma between 1985 and 2001. Age (years) and calendar year of Hodgkin lymphoma diagnosis (**closed circles**, ≥35 years, 1970–1984; **open circles**, ≥35 years, 1985–2001; **closed triangles**, <35 years, 1970–1984; **open triangles**, <35 years, 1985–2001).

significantly elevated compared with the general population (EAR = 4.6, 95% CI = 3.0 to 6.5; $P<.001$). For patients diagnosed with Hodgkin lymphoma before 1984, the EAR was slightly elevated after 15 years (EAR = 1.3, 95% CI = 0.4 to 2.6). Subsequent results are adjusted for time since Hodgkin lymphoma diagnosis and presented for the 5–9 year period.

Although risks were elevated for all groups, patients whose initial treatment included any chemotherapy, compared with RT alone, had a statistically significantly larger EAR of AML (EAR = 11.3, 95% CI = 8.5 to 14.7 and EAR = 5.4, 95% CI = 3.7 to 7.7, respectively; $P<.001$; Table 1). Excess absolute risks were higher for older patients (≥35 years versus <35 years) and for the earlier period (1970–1984 versus 1985–2001). The decline over calendar year, as measured by the difference in the EARs, was particularly apparent among patients who initially received any chemotherapy. Patterns of risk by age and calendar year of Hodgkin lymphoma diagnosis for the entire period of follow-up are summarized in Fig. 1.

To our knowledge, this is the first large, international population–based study of Hodgkin lymphoma patients to demonstrate an overall reduction, although not elimination, in the burden of AML over calendar year time. This decline likely reflects in part changes in chemotherapy (given initially or at relapse) that were implemented over the last few decades. Our results are consistent with reports of lower risks of AML among patients treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) compared with MOPP *(21–23)*. The positive association between EAR and age at Hodgkin lymphoma diagnosis may reflect in part the increase in population baseline risks for AML with increasing age. Because most of the excess risk is concentrated in the 10-year period following Hodgkin lymphoma diagnosis, age at Hodgkin lymphoma diagnosis and age at risk of AML are similar; it is therefore difficult to separate the individual effects of these variables.

Reports based on detailed treatment data suggest that AML risk is no longer elevated 10 or more years after the termination of chemotherapy for Hodgkin lymphoma *(2,24,25)*, although several reports may not have had adequate statistical power to evaluate risk in long-term survivors *(24,25)*. The persistence of increased EAR for over one decade in our series may reflect the effect of subsequent chemotherapy (e.g., at relapse).

Potential limitations of our study include those common to registry-based studies, such as incomplete treatment data and lack of detailed therapy information. Further, our estimates of EAR likely represent a minimal gauge of risk, because underreporting of secondary leukemia *(26,27)* has been observed in population-based cancer registries. It seems unlikely, however, that underreporting would be differential by initial treatment for Hodgkin lymphoma.

Our study also has several strengths, which include the large cohort size, inclusion of patients diagnosed with Hodgkin lymphoma over a 30-year period, and adjustment for time since Hodgkin lymphoma diagnosis. Also, our investigation is population-based.

In conclusion, the risk of AML following Hodgkin lymphoma has decreased statistically significantly over calendar-year time, likely due to modifications in chemotherapy. Analytic studies with detailed treatment data are required to correlate these decreases with changes in therapy and to better understand the long-term risk of AML after Hodgkin lymphoma.

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NOTES

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